REMARKS

Claim 11 is amended as supported by the specification at paragraph [0023]. Claims 13-14 and 19 are canceled. Claim 17 is amended to depend from claim 11 in view of the cancellation of claim 14.

Claims 1-10, 15, 16 and 18 are withdrawn from consideration.

No new matter is presented.

Response to Claim Rejection - 35 USC § 112

Claims 11-14, 17 and 19 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

According to the Examiner, the specification as filed does not provide adequate written description for the newly added limitations to claim 11. In this respect, the Examiner refers to paragraph [0023] of the specification, which was indicated as providing support for the amendment "not having benign prostatic hyperplasia or symptomatic prostatism".

Applicants respectfully traverse the rejection and submit that the present specification specifically mentions incontinence associated with prostrate hypertrophy or idiopathic pollakiuria (i.e., frequent urination) or incontinence accompanied with the same, i.e., prostrate hypertrophy. Thus, the present specification specifically teaches a positive recitation of treatment of incontinence and urinary frequency associated with prostrate hypertrophy at paragraph [0023]. Additionally, paragraph [0023] states that the recited combination is useful for the treatment of urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladders spasm, chronic or acute cystitis, chronic or acute

prostatitis or the like, which are disorders and conditions not associated at least with prostrate hypertrophy.

Moreover, paragraph [0055] teaches:

> … in benign prostatic hypertrophy (BPH), α1-ARs mainly distributing in smooth muscle of prostate and urethra increase. It is known that α1-AR blockers such as silodosin, tamsulosin, urapidil or the like improve the urethral resistance because the urethral smooth muscle is relaxed by their α 1-AR blocking activities. For example, the usefulness for dysuria associated with BPH on silodosin (see Patent Reference 2), for dysuria associated with BPH (see Patent Reference 3), urinary dysfunction associated with functional obstruction of lower urinary tract (see Patent Reference 4) and voiding dysfunction associated with neurogenic bladder (see Patent Reference 5) on tamsulosin, and for urinary dysfunction associated with neurogenic bladder on urapidil (see Patent Reference 2) have been reported, respectively. However, there are neither any reports that α 1-AR blockers have activities decreasing the intra-bladder pressure or prolonging the micturition interval nor any suggestions about a medicine comprising combination of an α 1-AR blocker and a compound represented by the general formula (I) in these references. In addition, in Patent Reference 6, it is mentioned that various drugs including a β3-AR stimulant, an α 1-AR blocker and the like can be used in combination for pain, inflammation or the like of urinary and sexual organs. But any combined use of a β3-AR stimulant and an α 1-AR blocker is not specifically described, and it is not also described that such a use is effective for the prevention or treatment of the urinary frequency and/or incontinence in the reference.

Thus, taken with the description in the specification and the knowledge available in the art, the specification provides adequate written description for at least treatment of patients having incontinence and urinary frequency associated with BPH, and treatment of patients having incontinence or urinary frequency not accompanied with prostrate hypertrophy such that treatment of patients having incontinence and urinary frequency not associated with BPH can be excluded.

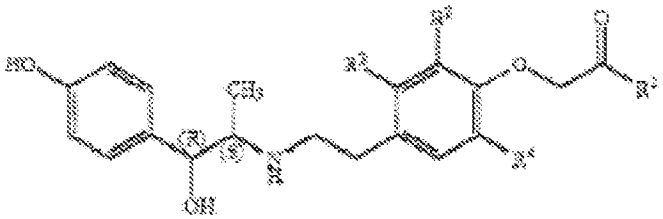
Notwithstanding the above and merely to facilitate and expedite prosecution, claim 11 is amended herein to recite a subject having urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladder spasm, chronic or acute cystitis, and chronic or acute prostatitis as disclosed in paragraph [0023] of the specification.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §112, 1st paragraph rejection.

Response to Claim Rejection - 35 USC § 103

Claims 11-14, 17 and 19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tanaka et al (WO 00/02846, cited as a functional language equivalent is U.S. 6,538,152) in view of Garvey et al. (U.S. 2002/0143007) as evidenced by Mesh Supplementary Data (2009; of record) and Guittard et al. (U.S. 6,262,115).

Tanaka et al is relied on as in the previous action as teaching the administration of the compound:



where R2 and R3 are ach lower alkyl groups and pharmaceutically acceptable salts thereof, for the treatment of urinary incontinence (abstract).

The Examiner cites Garvey et al as a new reference and asserts that Garvey et al teaches a method for the treatment of an overactive bladder with the administration of an alpha-adrenergic receptor antagonist such as KMD-3213 (claims 36 and 38). The usual doses of alpha-adrenergic

receptor antagonists are about 1 mg to about 100 mg per day, preferably about 0.5 mg to about 10 mg per day (paragraph [0256]).

Mesh Supplementary data is relied on as teaching that KMD-3213 is an alternative name for silodosin.

Guittard et al is also newly cited as teaching that involuntary urinary incontinence is also known as urge incontinence and overactive bladder (column 1, lines 55-56).

It is the Examiner' position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to administer silodosin (alpha-adrenoreceptor antagonist) in combination with ethyl(-)-2-[4-[2-[[(1S,2R)-2-hydroxy-2-(4- hydroxypheny1)-1-ethylethyl]amino] ethyl]-2,5-dimethylphenoxy]acetate in view of teachings of Tanaka et al and Garvey et al because each of the therapeutics have been taught in the prior art to be useful for the treatment of urinary incontinence. Further, the Examiner asserts that Guittard et al teaches that urinary incontinence is alternatively known as an overactive bladder.

Applicants respectfully traverse the rejection.

The cited references do not teach or suggest the presently claimed method of treatment of the frequency or urinary incontinence in a patient not having benign hyperplasia or symptomatic prostatism such as urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladder spasm, chronic or acute cystitis or chronic or acute prostatitis as recited in amended claim 11. Additionally, claim 11 is amended to recite administering a combination consisting essentially of a phenoxyacetic acid derivative represented by formula (I) and silodosin or a pharmaceutically acceptable salt thereof.

More specifically, (1) the teachings of Tanaka and Garvey et al do not provide a reason to a person having ordinary skill in the art to use silodosin alone or in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladder spasm, chronic or acute cystitis or chronic or acute prostatitis as recited in the present claims; and (2) the unexpected results obtained by the presently claimed invention rebut any *prima facie* case of obviousness that may have been set forth.

The teachings of Tanaka and Garvey et al do not provide a reason to a person having ordinary skill in the art to use silodosin in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladder spasm, chronic or acute cystitis or chronic or acute prostatitis.

As stated above, the Examiner relies on Garvey et al as teaching method for the treatment of an overactive bladder with the administration of an alpha-adrenergic receptor antagonist such as KMD-3213 (claims 36 and 38) and that the usual doses of alpha-adrenergic receptor antagonists are about 1 mg to about 100 mg per day, preferably about 0.5 mg to about 10 mg per day (paragraph [0256]).

However, Garvey et al discloses the use of compositions comprising (1) a nitrosated and/or nitrosylated α-adrenergic receptor antagonist; (2) an α-adrenergic receptor antagonist optionally substituted with at least one NO and/or NO_2 group, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase; and (3) an α-adrenergic receptor antagonist optionally substituted with at least one NO and/or NO_2 group and at least one vasoactive agent and

optionally at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. See paragraph [0242]. Thus, the combination of agents in Garvey et al is different from the combination of agents in the present claims.

The Examiner states that Garvey teaches a method for the treatment of an overactive bladder with the administration of an a-adrenergic receptor antagonist such as KMD-3213 (claims 36 and 38). However, claim 36 relates to a method for treating overactive bladder comprising administering a compound of claim 1, at least one compound that donates nitric oxide or the like (claim 17) and further at least one vasoactive agent (at least three compounds). Claim 38 relates to a composition comprising at least one a-adrenergic receptor antagonist and at least one compound that donates nitric oxide or the like (claim 37) and not to any specific condition such as overactive bladder. Thus, these claims neither disclose nor suggest anything about the presently claimed invention.

Additionally, although Garvey et al mentions urge incontinence and overactive bladder as conditions that may be treated, there is no example of such treatment and no guidance or suggestion as to which of the many potential combinations of agents suggested might have been considered for the treatment of these particular conditions amongst all of the conditions listed. The only *in vivo* examples in Garvey et al relate to sexual dysfunction (Figures 1-11) and do not employ a compound or composition within the scope of the present claims. There is no data supporting the effect of such a combination with respect to overactive bladder. Thus, one of ordinary skill in the art would not have been motivated to use silodosin for the treatment of urinary frequency or incontinence with a reasonable expectation of success based on the teachings of Tanaka and Garvey et al.

Mesh Supplementary data and Guittard et al fail to remedy the deficiencies of Tanaka and Garvey et al.

Furthermore, the present invention provides unexpectedly superior effects as previously discussed. Namely, in the micturition interval measurement as shown in Example 2 of the present specification, the inventors used the acetic acid-stimulated frequency model, which is a frequency model independent of the presence or absence of urinary obstruction. Therefore, the results on silodosin show the direct effect improving urinary frequency of silodosin, not a secondary effect by inhibiting contraction of urethra.

Thus, the teachings of the cited references, whether taken alone or in combination, do not provide a reason to a person having ordinary skill in the art to use silodosin in combination with a phenoxyacetic acid derivative (I) of the presently claimed invention for treating urinary frequency or incontinence in a subject having urinary frequency or incontinence accompanied with neurogenic bladder dysfunction, unstable bladder, bladder spasm, chronic or acute cystitis or chronic or acute prostatitis. For at least this reason, the present invention is not rendered obvious by the cited references.

In addition, the specific combination of silodosin and the phenoxyacetic acid derivative of the formula (I) of the present invention exerts the unexpectedly synergic effect. For this additional reason, the present invention is patentable over the cited references.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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